بسم الله الرحمن الرحيم

Armed Forces College of Medicine

AFCM

Treatment of Angina

Dr. Ghada Farouk Saleh

Assistant professor of Medical Pharmacology

Internal medicine specialist/ CU

Cardiopulmonary module

Lecture 2:

INTENDED LEARNING OBJECTIVES (ILO)

1) Explain the role of Ca channel–blockers as antianginal drugs
2) Explain the uses adverse effects and drug interactions of Ca channel -blockers as antianginal drugs
3) Explain the role of beta –blockers as antianginal drugs
4) Identify anti-platelets drugs.
5) Identify other drugs used in anginal treatment.
6) Identify favorable and unfavorable anti-Anginal Combinations

2- Ca channel Blockers

Classification:

1- Non- Dihydropyridines heart inhibition > VD (Verapamil, diltiazem).

2- Dihydropyridines VD > heart inhibition

a- Long Acting: Amlodipine.

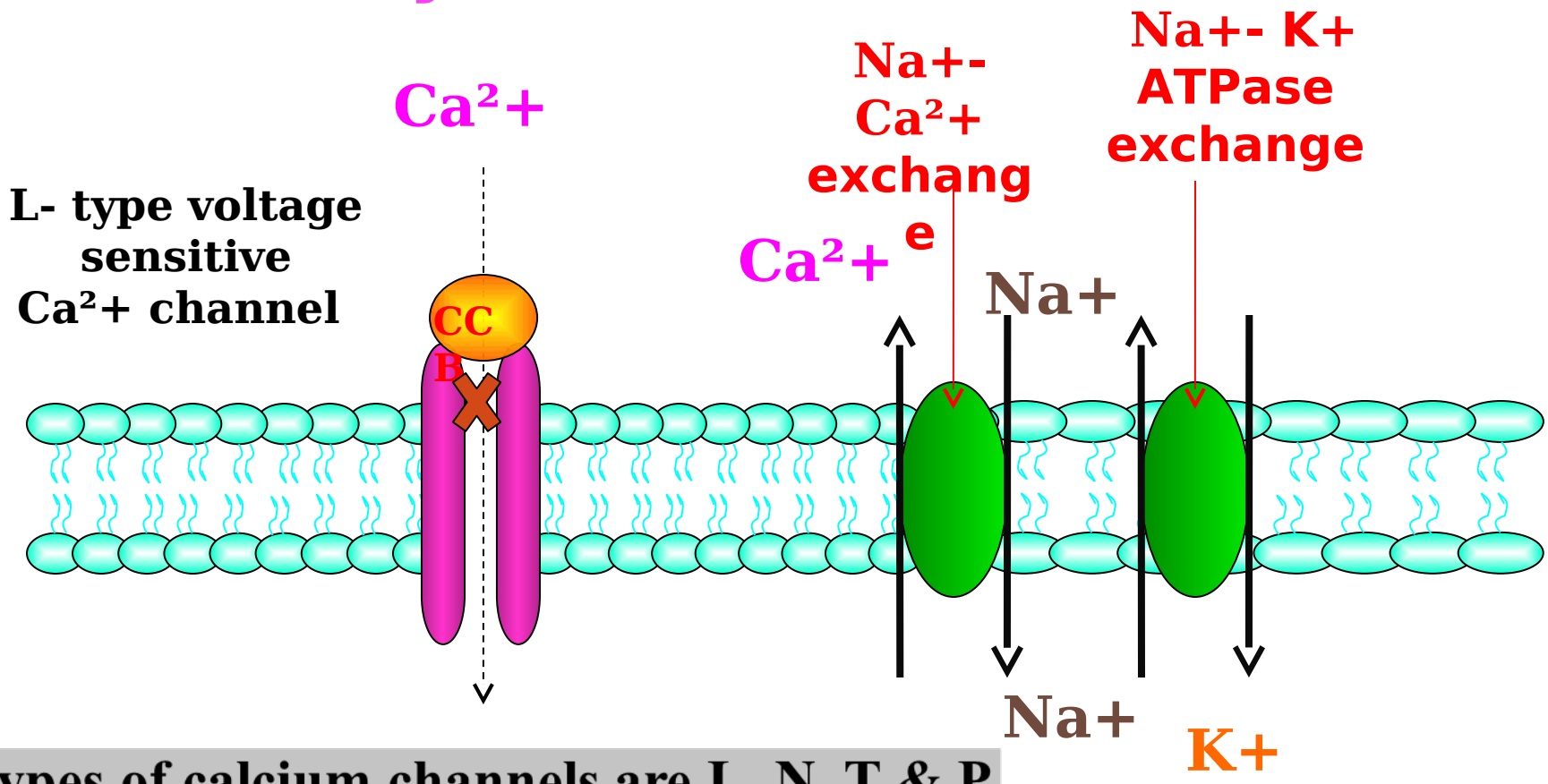
b- Intermediate Acting: Nifedipine, Nitrendipine, Felodipine & Isradipine.

c- Short Acting: Nicardipine & Nimodipine.

Pharmacokinetics

	Verapamil	Diltiazem	Nifedipine
1- Oral Absorption :	Well	Well	Well
2- Oral bioavailability :	Low (20 %)	Moderate (40 %)	High (60 %)
3- First pass met. :	High	Moderate	Little
4- Binding to plasma proteins:	High (90 %)	High (80 %)	High (90 %)
5- Fate :	- Hepatic metabolism - Renal & biliary excretion	- Hepatic metabolism - Renal & biliary excretion	- Hepatic metabolism - Renal & biliary excretion
6- t ½ :	4 hours	4 hours	2 hours

Pharmacodynamics



Types of calcium channels are L, N, T & P.

Mechanism of Action:

Pharmacodynamics

I- Mechanism of Action:

1- They **block Voltage-dependent L-type** calcium channels present in Heart, Blood vessels and Smooth muscles.

2- **They ↓ Ca2+ influx into:**

a-

Cardiac muscle → Cardiac inhibition

b-

Blood vessels → Arteriolar VD

c- smooth muscle relaxation

2-Pharmacological Action:

A) C. V. S.:

Verapamil & Diltiazem (inhibit Heart > VD):

1- POWERFUL CARDIAC DEPRESSANT:

a- **-ve Chronotropic Effect = inhibit SAN = Bradycardia**:

- Long Diastolic Perfusion Time for the coronaries.
- Antagonizes Tachycardia induced by Nitrates.

b- -ve Inotropic Effect = decreases Contractility:

- Decreases Cardiac work & Oxygen consumption.
- Contraindicated in Heart Failure.

c- **-ve Dromotropic effect = decreases AV Conduction: VD**

- Contraindicated in Heart Block.
- NOT Combined with B-Blockers or Digitalis.

d- **Decreases Automaticity** ⇨ decreases Ectopic Focus Formation

(Class IV Anti-Arrhythmic).

2- Less peripheral V.D. than Nifedipine BUT POTENT Coronary V.D.

2-Pharmacological Action:

2- Nifedipine (V.D. > Inhibition of Heart):

1- POWERFUL V.D. (ARTERIAL > Vein in contrast to Nitrates):

a- **Potent Arterio-Dilator** ↓ TPR ↓ AFTER-LOAD ↓ Cardiac Work &

b- **Weak Veno-dilator** Less ↓ VR ↓ Preload O2Consumption.

c- Coronary VD: BUT VD of SMALL coronaries on the non-ischemic area may steal the blood from the atherosclerosed area → Coronary Steal Phenomenon

d- **Hypotension** :Reflex stimulation of Sympathetic system → Tachycardia → Short Diastolic Filling. **Better ADD B-Blocker.**

Better not used ALONE with Nitrates.

2- Very Weak Myocardial Depressant:

a- **Does NOT inhibit SAN.** It even causes TACHYCARDIA.

b- **Does NOT inhibit AVN**. Allowed in Heart Block.

c- **Minimal -ve Inotropic** → COP is maintained or may increase → Allowed in HF.

d- It is **NOT an Anti-arrhythmic.**

2-Pharmacological Action:

B) Other Actions of CCB:

a- Decreases Platelet aggregation mainly in vitro.

b- Smooth muscle relaxation e.g. Bronchial, Biliary, GIT, Urinary & Uterine.

c- Endocrine: Verapamil decreases insulin release in large dose.

d- Skeletal muscle: No effect

(*does not affect on skeletal muscles because there is no Ca2+ channels in skeletal muscles & these muscles depend on exogenous Ca2+ in their contraction not on endogenous Ca2+)*

Therapeutic Uses of Ca channel blocker

1- Prophylaxis of all types of Angina.

a- Verapamil & Diltiazem:

- Indicated specially in Angina + Cardiac arrhythmia.

b- Nifedipine:

- Indicated specially if angina + Hypertension or Bronchial asthma.

a. Coronary VD → Treat **Variant Angina.**

b. Treat **Effort Angina & Unstable Angina.**

- Decreases Cardiac Work & O_2 consumption
- Powerful arteriolar VD → Decreases TPR → Decreases after-load
- Mild Veno-Dilator → Mild decrease of VR → Mild decrease of Preload.
- Decrease Platelet aggregation.

2- Cardiac Arrhythmias especially Verapamil:

a- IV verapamil is antiarrthymic supraventricular tachycardia.

b- decreases HR in atrial flutter & fibrillation.

Therapeutic Uses of Ca channel blocker

3- Hypertrophic Obstructive Cardiomyopathy with subaortic stenosis:
Verapamil & Diltiazem -ve ino + -ve Chrono More filling & arterial VD
More emptying

4- Hypertension especially Nifedipine Arterial VD decreasesTPR
decreases Bl.p.

5- P.V.D. especially D.H.P. group.

6- Cerebral spasm in response to subarachnoid hemorrhage: Nimodipine.

7- Migraine headache: Nimodipine & Flunarizine.

Adverse Effects of Ca channel blocker

1- Headache & flush.
2- Heart:
a- Verapamil & Diltiazem
- -ve Inotropic Heart failure.
- -ve Chronotropic Bradycardia.
- -ve Dromotropic Heart Block.

NOT combined with B- Blockers.

b- Nifedipine Tachycardia & may aggravate angina by its steel phenomena.

3- Hypotension.
4- Constipation specially Verapamil. ⟶
5- Reversible liver impairment.
6- Ankle edema specially Nifedipine

Drug interactions of CCB.

a- Verapamil ↓ Renal excretion of Digoxin.

b- Verapamil + β-Blocker → Severe Cardiac depression.

c- Nifedipine + Nitrates → Severe Hypotension & Tachycardia

Other Calcium Channel Blockers

1- Flunarizine:

a- Prophylaxis of Migraine headache.

b- Peripheral vascular diseases.

2- Indapamide:

a- Related to Thiazide Diuretics.

b- Used in Sub-diuretic dose in treatment of Hypertension.

c- Advantages:

- Minimal effect on Electrolytes, Glucose, Uric acid & Lipid metabolism.
- Long Acting Used 2.5 mg ONCE/Day.
- Depends on Biliary excretion, so allowed in patients with Renal impairment.

3- Amiodarone Anti-Anginal + Class III Anti-arrhythmic.

3- B- Blockers

1- All B-Blockers (selective or non-selective) are effective in angina pectoris:

a- Better use B-Blockers without Intrinsic Sympathetic Activity.

b- Non-selective: Propranolol & Nadolol.

c- Selective B1-Blockers e.g. Atenolol, Metoprolol & Bisoprolol.

d- Vaso-dilator B-Blockers e.g. Carvedilol

2- They do NOT produce coronary V.D. Non-selective B-Blockers may cause V.C. of normal coronaries Shift & Redistribution of coronary flow to ischemic area

B-Blockers

3- *Desirable*

❶-↓ H.R. → Resting HR 50-60 b/min or Max HR 100-120 b/min.

❷- ↓ Contractility.

❸-Long use → Anti-hypertensive → ↓ After-load.

- ↓ Cardiac work & ↓ O_2- Consumption:

tachycardi

Anxiety

Exercise

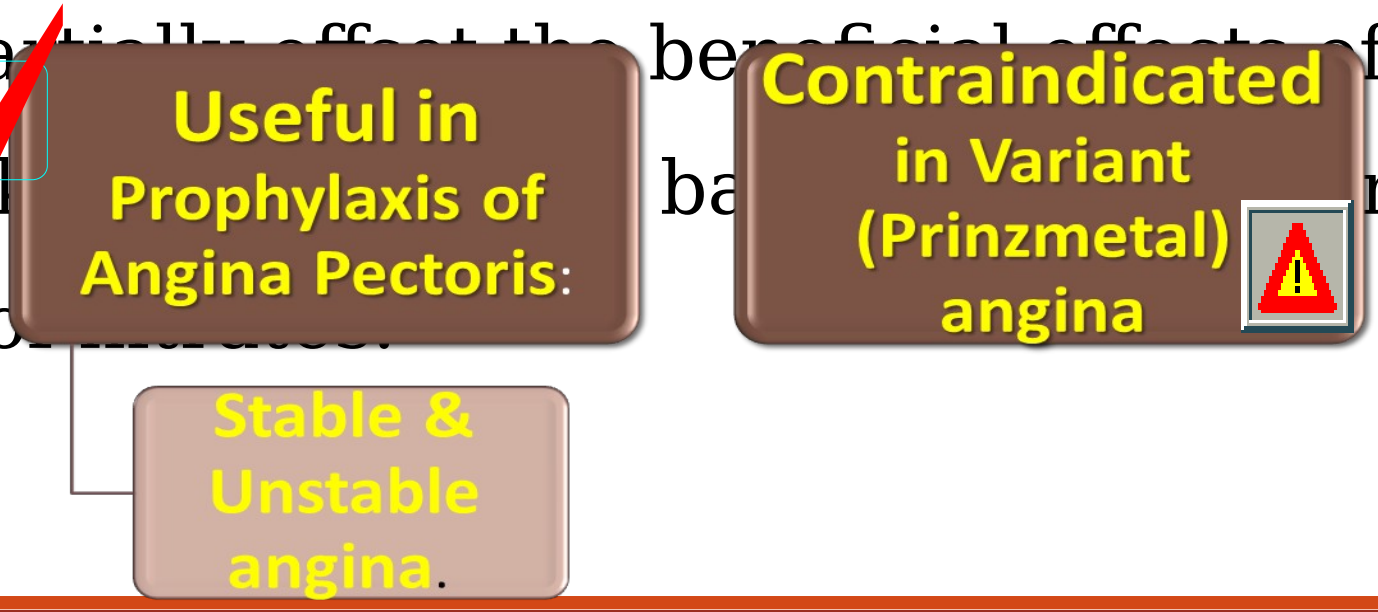
+ Nitrates
Nifedipine

4- ***Undesirable*** effects: Bradycardia

→

a- Long diastole → ↑ E.D.V. → ↑ Preload. - ↑ O2-needs

→ Pa be f B-Bloc ba mitant use o



Drug Group	Decrease Cardiac Work			Coronary VD
	Arterial VD decrease After load	Venodilator decrease Preload	Heart -ve Inotropic & -ve Chronotropic	
1- Nitrates		+ + +		+ + +
2- Calcium channel blockers	+ + +		+++ (Verapamil)	+ + +
3- Beta-Blockers			+ + +	

IV- Anti-Platelet Drugs

1- Aspirin in SD :(75–150 mg) →

↓ Platelet TXA-2. Also treats Nitrate-induced headache

→ ↓

2- ADP-Receptors Blockers: Ticlopidine & Clopidogrel.

3- GP IIb/IIIa-Receptors Blockers:

Abciximab & Tirofiban

A) Favorable Anti-Anginal Combinations:

βeta-blocker+ Nitrates:

Nitrates: Coronary VD + Veno-dilator + decrease Preload + reflex stimulation of

Sympathetic system leading to increase Contractility & Tachycardia and Shorten Diastolic Coronary Perfusion Time.

βeta-blocker: decreases cardiac work & O2-consumption, increases diastolic coronary perfusion time and prevents tachycardia induced by nitrates.

Nitrates+ Verapamil or diltiazem

Nitrates: Coronary VD + Veno-dilator + decrease Preload+ increase HR + decrease diastolic time.

Verapamil : Coronary VD+ Arterio-dilator+ decreases afterload &HR+ increases diastolic time.

βeta-blocker + Nifedipine or amlodipine:

Nifedipine or amlodipine:

a- Potent Arterio-Dilator decreases TPR & After-load.

b- Weak Ven o-dilator less decrease in VR & Preload→ decrease in Cardiac Work & O2 Consumption

c- Hypotension → Reflex stimulation of Sympathetic system → Tachycardia → Short Diastolic Filling

Beta-blockers :

Decreases cardiac work & O2-consumption, increases Diastolic coronary perfusion time and prevents tachycardia induced by nifedipine or amlodipine.

Beta-blocker +Nitrates +Nifedipine or amlodipine: discussed previously

B) Unfavorable Anti-Anginal Combinations:

1- Nitrate + Nifedipine Severe Hypotension & Tachycardia.

2- B-Blockers + Verapamil Severe Cardiac Inhibition.

3- Do NOT use 2 drugs of the same class in the same line of treatment.

Other Anti-Anginal Drugs

1- Nicorandil

1-It has a dual mechanism of action:

a- Opens ATP-dependent $K^{\pm}$-Channel leads to **hyperpolarization**

I. Heart ---------- decrease cardiac work

II. Blood vessels ---------- vasodilatation

b- Nitrate-like, Release NO = **Nitrodilator.**

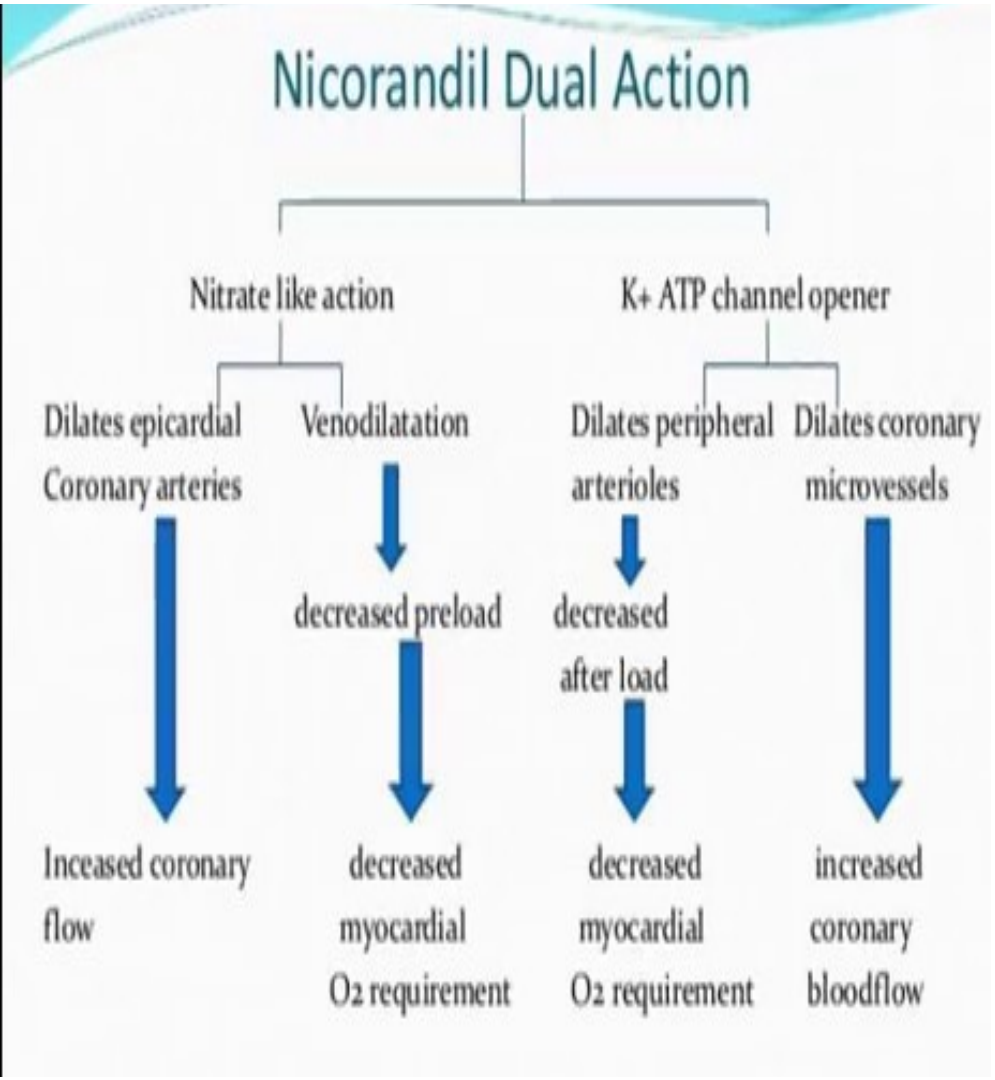
2-V.D. of Normal Large Epicardial coronaries.

3-Used Orally for treatment of Angina & Heart failure

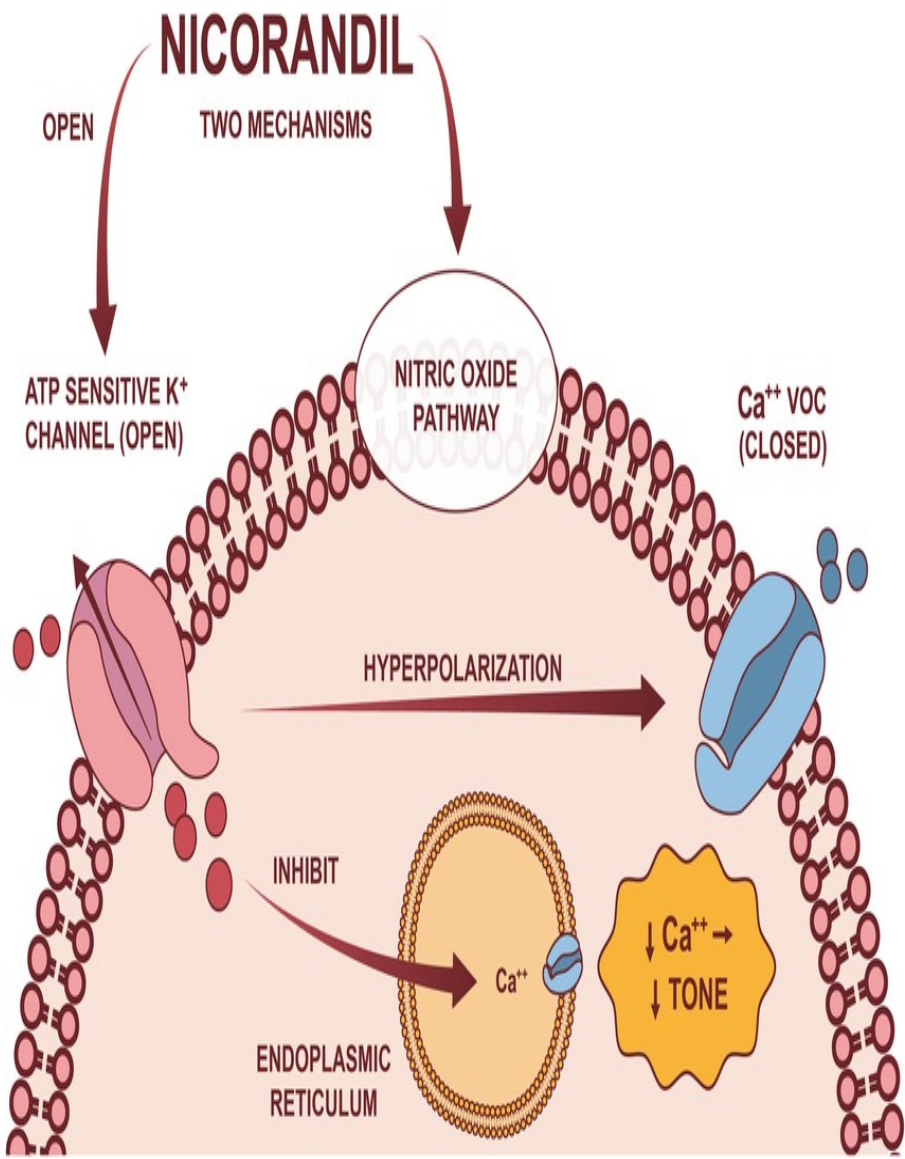
4-The vasodilator action is partly antagonized by K+ channel blocker **glibenclamide** (antidiabetic drug)

5- No tolerance BUT may produce Headache.

6- **Contraindicated in** cardiogenic shock, left ventricular failure, and hypotension.



https://i.ytimg.com/vi/ZAGzUL8FxPg/hqdefault.jpg



https://www.researchgate.net/publication/347857784/figure/fig2/AS:998443048783884@1615058781964/

Other Anti-Anginal Drugs

2- Trimetazidine

❶- anti-Ischemic and cytoprotective

❷- It is metabolic agent which improves myocardial glucose utilization through a reduction in fatty oxidation and a stimulation of glucose oxidation. *The heart favors fatty acids as a substrate for energy production. However, oxidation of fatty acids requires more oxygen per unit of ATP generated than oxidation of carbohydrates.*

❸- Decreases free radical production.

❹- Decreases lactate production, and intracellular acidosis.

❺- Decreases intracellular Ca overload.

❺- Used orally in effort angina.

Other Anti-Anginal Drugs

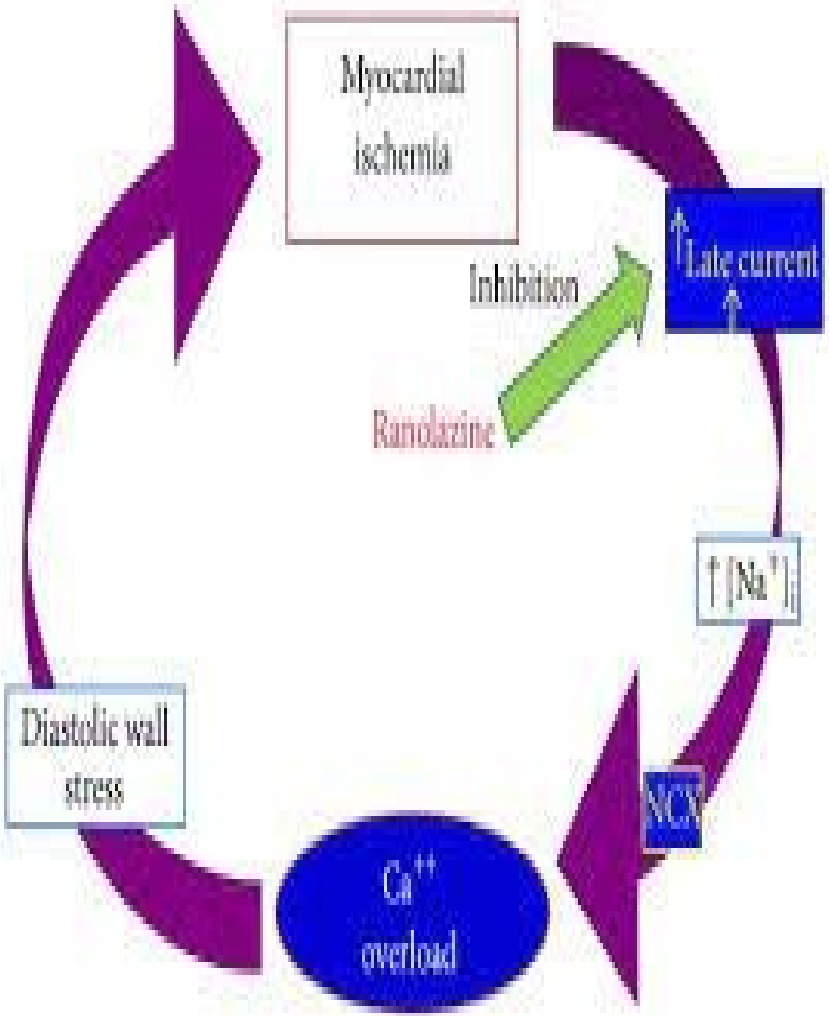
3- Ranolazine

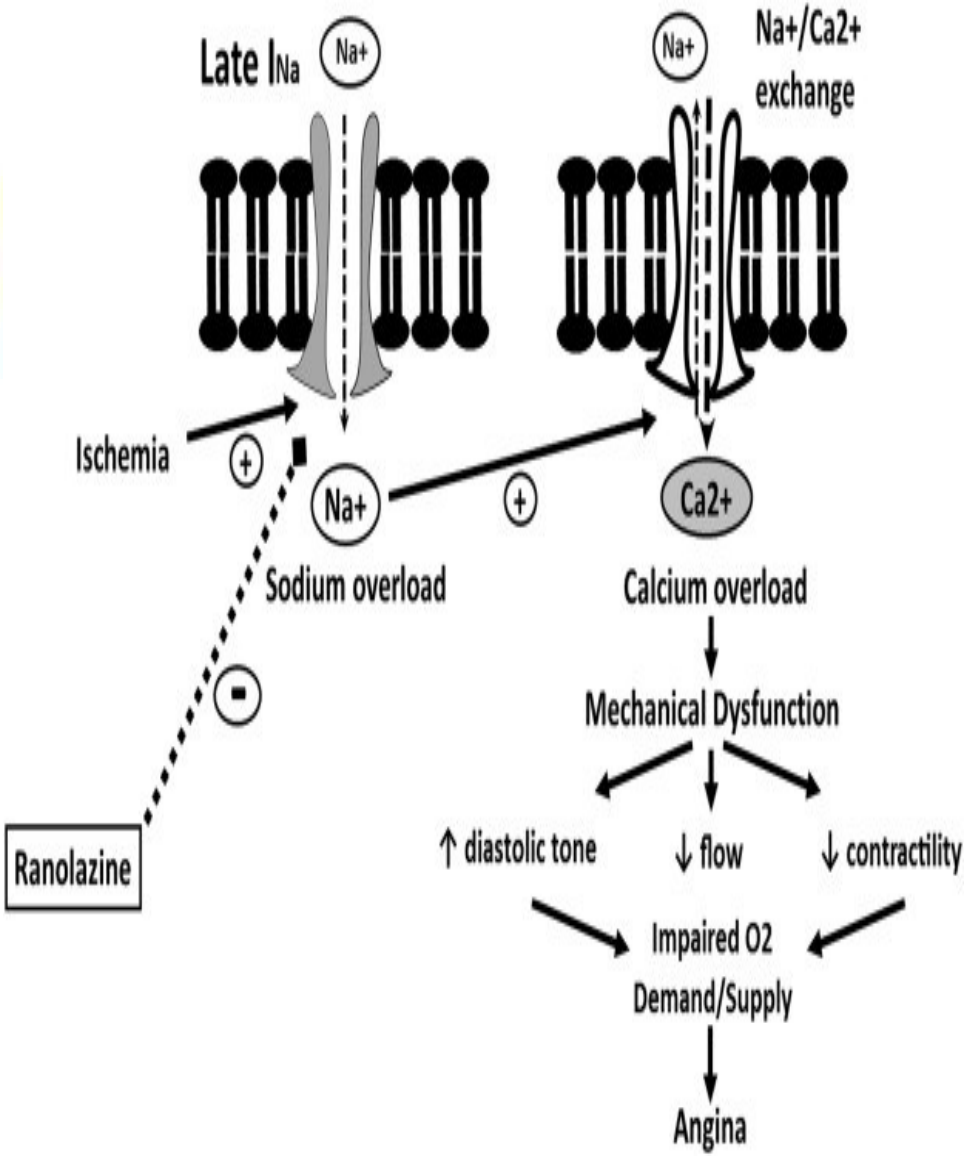
1. Prevents abnormal opening of the late Na+ channels in the myocardium which indirectly facilitates Ca2+ entry.

2. Reduction in Ca2+ overload in the myocardium during ischemia may play an important role in the cardioprotective action of ranolazine leading to:

a. decreases myocardial contractility

b. decreases Myocardial oxygen demand & increases blood flow to myocardium





https://jpet.aspetjournals.org/content/jpet/346/3/343/F1.large.jpg

Other Anti-Anginal Drugs

4- Ivabridine

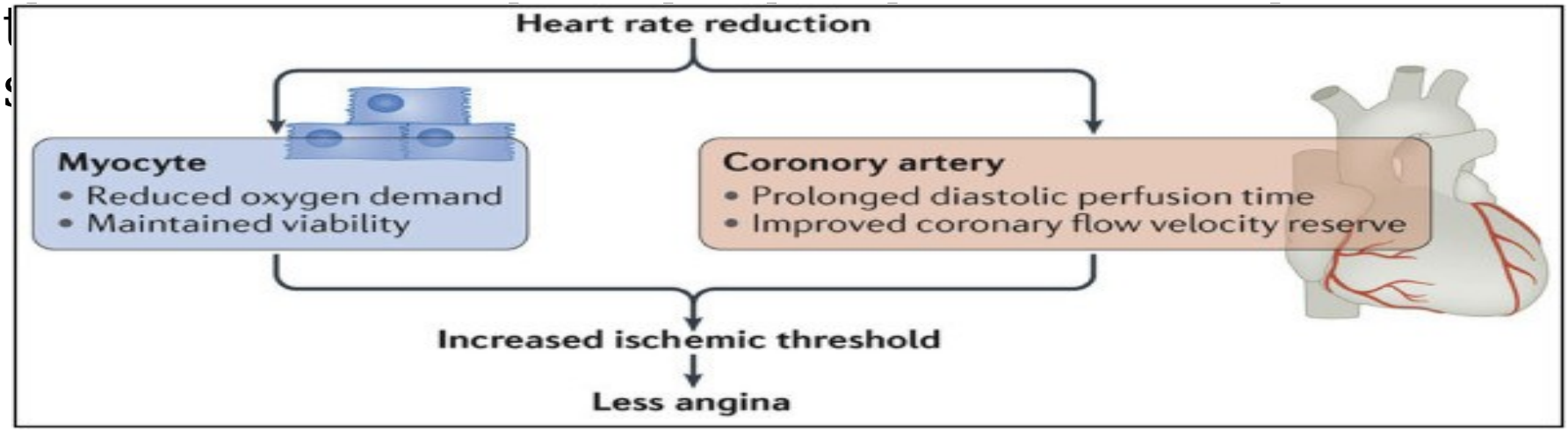
treatment of chronic stable angina pectoris in adult patients:

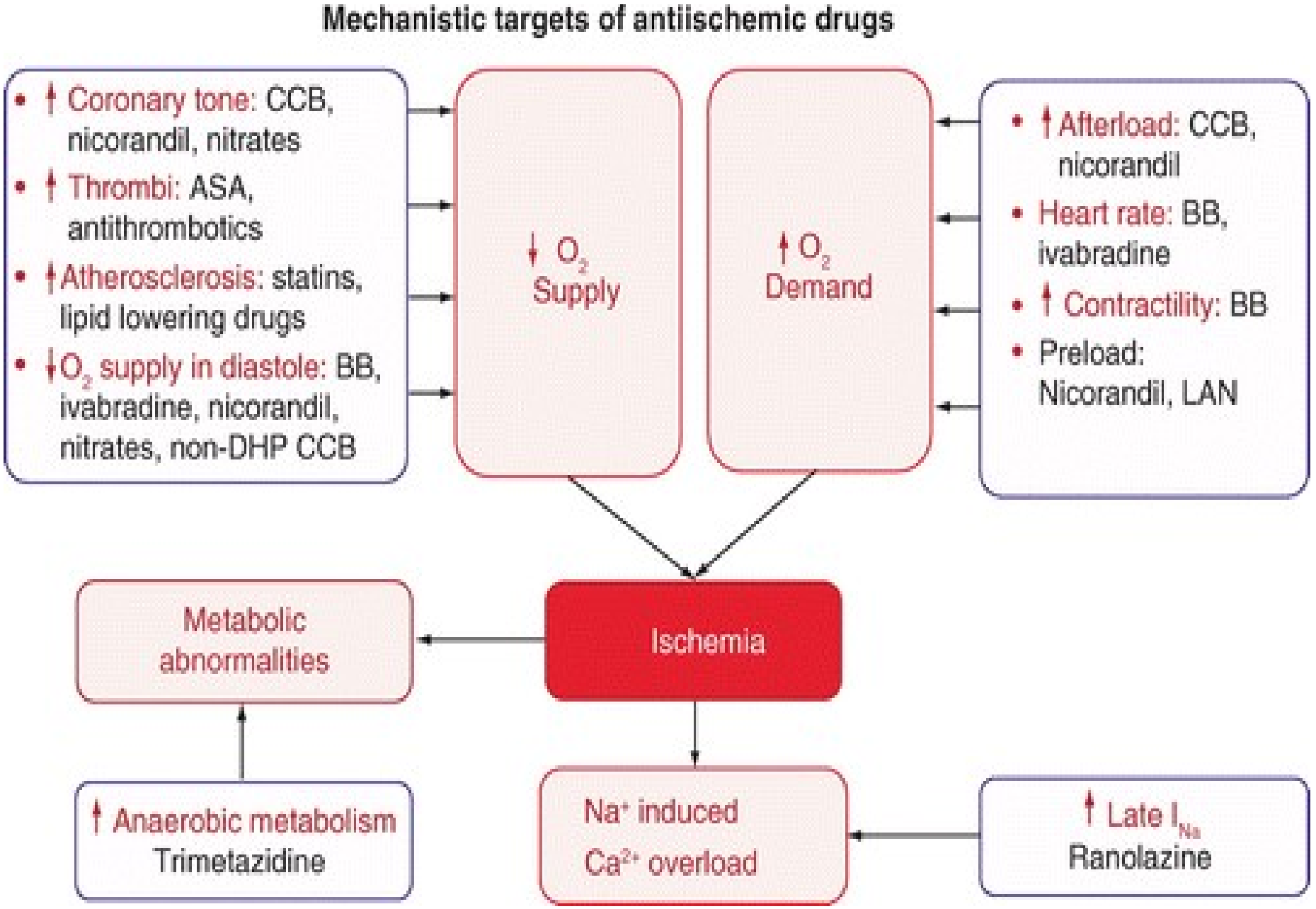
A- with normal sinus ryhythm

B- with heart rate ≥ 70 / min

Mechanism of action:

Selective and specific inhibition of the cardiac pacemaker funny channels current that controls




Mechanistic targets of antiischemic drugs
• ↑ Coronary tone: CCB, nicorandil, nitrates
• ↑ Thrombi: ASA, antithrombotics
• ↑ Atherosclerosis: statins, lipid lowering drugs
• ↓ O_2 supply in diastole: BB, ivabradine, nicorandil, nitrates, non-DHP CCB
↓ O_2 Supply
↑ O_2 Demand
• ↑ Afterload: CCB, nicorandil
• Heart rate: BB, ivabradine
• ↑ Contractility: BB
• Preload: Nicorandil, LAN
Metabolic abnormalities
Ischemia
↑ Anaerobic metabolism
Trimetazidine
Na^+ induced
Ca^{2+} overload
↑ Late I_{Na}
Ranolazine

1- Mention the mechanism of action of verapamil?

2- Identify the undesirable effects of B blockers as antianginal drugs?

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Neal L. Benowitz, MD. In: Katzung BG (ed.). (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

Cardiopulmonary module

Thank You